nodes in the neck. Blood: haemoglobin 63%; W.B.C. 2,900 (98% lymphocytes, 2% polymorphs); platelets 20,000; bleeding-time (Duke) 30 minutes; coagulation time 4 minutes. Sternal marrow (April 20): complete absence of erythropoietic and granulopoietic cells and of megakaryocytes. The cells present were mostly lymphocytes and plasma and reticulum cells; and the marrow picture was typical of aplastic anaemia. In her final illness the patient was treated with penicillin, streptomycin, fresh blood transfusion, and steroids; but she died five days later with signs of severe pulmonary infection.

Post-mortem Examination.—The body was adequately nourished and slightly jaundiced, with scattered purpuric spots. There were scattered petechiae on the pericardium and on mucous membranes, with haemorrhagic consolidation in the lungs and pleurisy on the surface of the lower lobes. The spleen was firm and dark, the marrow of vertebrae appeared normal, but the femoral marrow was pale. The right lobe of the thyroid was slightly enlarged.

COMMENT

The evidence suggests that, in this patient, aplastic anaemia was due to the treatment with potassium perchlorate. The steroid therapy might have obscured the onset of symptoms resulting from toxic action on the marrow or it might possibly have contributed to its development. Corticosteroid therapy is usually regarded as being of value in the treatment of aplastic anaemia, although aplastic anaemia has been attributed to corticotrophin injections (Snively *et al.*, 1953) and agranulocytosis has been attributed to prednisolone (Rokseth, 1960). We have encountered no other serious side-effects in the treatment of some 50 patients with potassium perchlorate alone. One patient receiving both carbimazole and potassium perchlorate developed agranulocytosis.

A woman of 48 presented with a two-year history of marked loss of weight, dyspnoea, and auricular fibrillation, and with a massive vascular and nodular goitre estimated to weigh 300 g. She had had a partial thyroidectomy for hyperthyroidism 20 years before and had delayed seeking treatment as she feared a further operation. In view of her massive goitre she was thought unsuitable for surgery and was given carbimazole 15 mg. three times daily and potassium perchlorate 200 mg. three times daily; her cardiac condition was controlled with digoxin. She improved rapidly, but after 30 days' treatment became seriously ill with a sore throat, fever, and a peripheral blood count typical of agranulocytosis; a sternal marrow biopsy done some days later showed appearances compatible with recovering agranulocytosis. On withdrawal of antithyroid drugs and treatment with antibiotics, potassium iodide, and blood transfusion she recovered, and was later treated satisfactorily with radioiodine therapy.

Carbimazole was given to this patient in dosage larger than average on account of her severe disease and massive goitre, and may therefore be the most suspect toxic agent in this case. Serious blood dyscrasias are uncommon when carbimazole is administered in doses of 30 mg. daily or less (Burrell *et al.*, 1956). But we have seen one death from agranulocytosis in a woman of 52 treated for hyperthyroidsm with carbimazole in a dose of 30 mg. daily for five weeks.

Although agranulocytosis is a well-known complication of antithyroid drug treatment, aplastic anaemia has been seldom recorded and has not previously been attributed to potassium perchlorate in any report in the medical press.

Aplastic anaemia due to treatment with carbimazole was reported by Richardson *et al.* (1954) and by Burrell (1956) with fatal outcome in both patients. Aplastic anaemia due to treatment with methimazole, from which the patient recovered, was reported by Levine and Rosenberg (1954).

It would seem possible that aplastic anaemia may occur especially in patients in whom the recognition of the toxic side-effects has been delayed and the drug has not been promptly withdrawn.

The occurrence of aplastic anaemia in our patient suggests that this condition may be encountered in future with the more widespread use of potassium perchlorate as an antithyroid agent. Although when doses smaller than 1,000 mg. daily are used toxic side-effects are thought to be uncommon (Crooks and Wayne, 1960; Morgans and Trotter, 1960), further experience may reveal that small doses are occasionally hazardous.

Even after repeated verbal warnings concerning the possible side-effects of antithyroid agents, intelligent patients may fail to report for blood examination as they have been requested to do in the event of ill-health. A suitably worded card and a clearly labelled container stating the details of the drug being taken might help the patient and practitioner.

The early recognition of the toxic side-effects and the prompt withdrawal of the drug may contribute to avoiding the serious toxic effects.

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Fatal Aplastic Anaemia after Treatment of Thyrotoxicosis with Potassium Perchlorate

Experience during the past six years has shown potassium perchlorate to be as effective an antithyroid agent as the more commonly used organic drugs methylthiouracil and carbimazole (Morgans and Trotter, 1954; Godley and Stanbury, 1954; Smellie, 1957; Fairhurst and Hollingworth, 1958; Crooks and Wayne, 1959; Cook and Hawe, 1960; *Brit. med. J.*, 1960). The incidence of serious side-effects so far reported from its use has been low, and includes only two cases of agranulocytosis, each of which recovered, but the occurrence of a related aplastic anaemia has not hitherto been described.

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CASE REPORT

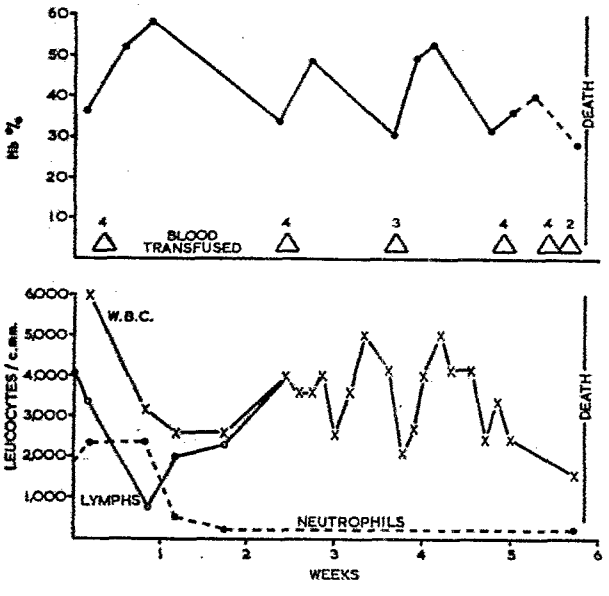
A woman aged 29 presented with characteristic signs of thyrotoxicosis of moderate severity, confirmed by radioactive iodine studies using a diagnostic dose of 25 microcuries. No history of previous blood disease was given, and although no blood count was done at this stage her mucous membranes were of normal colour.

Treatment was begun with oral potassium perchlorate 1 g./day, given as 400 mg. morning and evening and 200 mg. midday. A month later she showed clinical improvement of thyrotoxic features, so the drug was continued in the same dosage for a further two months. At her next attendance she had gained 7 lb. (3,175 g.) in weight, but complained of fatigue and generalized aching pains; she had a mildly myxoedematous appearance, so the dosage was

reduced to 200 mg. three times a day. A blood count was not made at this time, but no appearance of anaemia was observed.

A month later, however, she showed symptoms and signs of a gross anaemia of rapid onset. Some fever and puffiness of the face and feet had been noted, with claudication in the legs; but sore throat, cough, and skin lesions were absent, nor was there any evidence of gastro-intestinal or other bleeding.

On admission next day the haemoglobin was 37%, but apart from clinical signs of anaemia routine physical examination was negative. Investigations carried out on admission were as follows: blood count: haemoglobin, 5.5 g./100 ml. (37%); erythrocytes, 1,700,000/c.mm.; colour index, 1.1; P.C.V., 15%; M.C.H., 32 $\mu\mu$g.; M.C.V., 88 cubic microns; M.C.H.C., 37%; reticulocytes, 0.8% of red cells, platelets, 29,000/c.mm., leucocytes, 6,000/c.mm. (neutrophils 38%, eosinophils 1%, lymphocytes 57%, monocytes 4%). The red cells showed moderate anisocytosis and slight poikilocytosis, and appeared normochromic. Platelets appeared reduced in the film. Direct Coombs test was negative in all dilutions. Plasma proteins and electrophoretic analysis were normal. No abnormal pigments were detected. Marrow aspirate: (1) film showed that nucleated red cells were almost completely absent; there was some suggestion that the granulocyte series, which appeared abundant, showed a shift to the left. (2) Section (H. and E.) showed



a hyperplastic marrow with some islands of round-cell infiltration, probably lymphocytic. Megakaryocytes were present, although some seemed to be degenerate.

On the results of these investigations and the preceding history a diagnosis of aplastic anaemia was made.

A slow transfusion of 4 pints (2.3 litres) of compatible blood brought general improvement and a rise of haemoglobin to 58%. Reticulocyte response was absent, as also after subsequent transfusions. Prophylactic intramuscular and, later, oral penicillin was given, and prednisone 20 mg. t.d.s. was begun 10 days after admission. No marked improvement occurred, the haemoglobin falling to 36% two weeks after transfusion, with a relapse of weakness and malaise. Slight epistaxis occurred at intervals, and the subsequent menstrual period was unduly prolonged and heavy. A striking neutropenia was noted a week after admission, with a low platelet count.

During the next four weeks transfusion of 3–4 pints (1.7–2.3 litres) of fresh blood was repeated on three occasions (see Chart), each being followed by an immediate improvement in the general state and haemoglobin level, but with subsequent rapid intensification of anaemia and weakness. Skin haemorrhages, epistaxis, and haematuria became troublesome features. No jaundice was present. Three days after the fourth transfusion shivering occurred, with sore throat and fever of 100° F. (37.8° C.), followed by dry cough and a progressive worsening of illness. Intensive intravenous chemotherapy with penicillin and tetracycline was given. The haemoglobin level fell to 26%, still without evidence of jaundice. Two days after the onset of the cough and sore throat a sudden increase of fever to 104–106° F. (40–41.1° C.) occurred, with rapid deterioration, rigors, and worsening of unproductive cough and dyspnoea.

It was presumed that the patient had succumbed to an acute intercurrent septicaemic infection, although blood culture showed no growth. Chemotherapy was intensified to a dosage of 50 to 80 mega-units of penicillin daily, by intramuscular and intravenous routes, combined with intravenous tetracycline, and yet a further transfusion of 6 pints (3.4 litres) of fresh blood was given. Slight icterus was noted for the first time, coincidently with the abrupt rise of fever, and became progressively deeper. A rapid decline set in, progressing to stupor and coma, in which state she died 36 hours later with accompanying deep jaundice. The latter was thought to be secondary to the terminal infection, the direct Coombs test remaining negative throughout. The course of blood changes is shown in the Chart.

Necropsy (Dr. D. C. Caldwell) revealed a generalized deep jaundice, with multiple petechial haemorrhages into the skin, pericardium, mesentery, gastro-intestinal mucosa, and pelvic mucosa of the left kidney. Both lungs showed recent multiple small infarcts. The lymph nodes appeared normal; the spleen was firm, rubbery, and congested. The bone-marrow in the sternum, vertebrae, ribs, and upper end of femur was almost non-existent. Abundant Gram-positive cocci were present in sections from some of these areas.

Histological examination of the bone-marrow showed it to be virtually aplastic, but there were small islands of cellularity consisting of lymphocytes, reticulum cells, and a few eosinophils. There was no demonstrable marrow activity. The thyroid sections showed some acinae to be collapsed and crowded together, others markedly dilated, with areas of haemorrhage and a generalized increase of vascularity. The acinar epithelium was pale and vacuolated, colloid being almost completely absent, while some dilated acinae showed papillary protrusions.

The ante-mortem investigations, necropsy, and histology showed the course and sequelae of a fulminating aplastic anaemia.

Discussion

We traced 818 recorded cases treated with potassium perchlorate, and, overall, 36 (4%) toxic reactions were found. There was general agreement regarding its lessened liability, compared with the organic drugs methylthiouracil and carbimazole, to produce early minor sensitivity reactions, an important factor being the dosage employed. Morgans and Trotter (1960), for example, in 247 treated cases observed only 3% of toxic reactions with a dose of 400 to 1,000 mg. a day, but 18% using 1,200 to 1,600 mg. daily; while in a similar series of 204 cases Crooks and Wayne (1960) found an incidence of 2% and 16% respectively in the two dosage groups.

Hitherto, the general pattern of toxic reactions from potassium perchlorate has been of familiar type, with skin rashes, gastro-intestinal disturbances, and pyrexia, with sore throats, either singly or in combination, developing after two or three weeks' treatment. Less frequently lymphadenopathy and neutropenia have occurred.

Two cases of agranulocytosis and two of marked neutropenia have so far been described. Of these, Crooks and Wayne's case of agranulocytosis occurred

during the third week of treatment with 1,500 mg. daily, the peripheral blood and bone-marrow being otherwise normal, with a rapid recovery on suspending the drug. Southwell and Randall (1960) recorded the development of agranulocytosis and thrombocytopenia on the twelfth day of treatment with 1,000 mg. of potassium perchlorate daily, unaccompanied by red-cell changes, with recovery within two weeks of suspending treatment. Each of these patients showed concurrent fever and general toxic symptoms. Murray (1959) has described a third case with similar varied toxic reactions, the dose given being 1,200 mg. a day over a period of three weeks, a neutropenia of 800/c.mm. being observed. A further (unpublished) case under the care of Dr. Harold Lambert has been noted by Morgans and Trotter (1960), in which a severe leucopenia developed within two weeks of beginning potassium perchlorate in a dosage of 1,600 mg. daily.

The case here recorded presented with a previously unsuspected severe anaemia and moderate neutropenia after a period of treatment of just over three months. The anaemia rapidly progressed to a red-cell aplasia with thrombocytopenia, and the neutropenia to an agranulocytosis, giving the full picture of aplastic anaemia about one week after admission, though probably between two and four weeks after the onset of the anaemia. The haemorrhagic complications began to appear about two weeks after admission, and were followed by a thrombocytopenia, increasing in severity prior to the terminal infection.

Aplastic anaemia occurs either as a primary or idiopathic disease, or secondarily to exposure to a substance toxic to bone-marrow. In the idiopathic form the aplasia is rarely a total one, some degree of cellularity of the bone-marrow usually remaining, in contrast to the nearly complete absence commonly found in the secondary types and in the case under consideration. Reviewing the possibility in this patient of secondary causative factors of aplastic anaemia other than potassium perchlorate, thyrotoxicosis itself is not so recognized, and we feel that any aetiological relationship to the giving of 25 μc. of radioactive iodine for diagnosis is too remote for serious consideration, while there was no known history of recent exposure to any other drugs accepted as toxic to the bone-marrow. In this fatal case, therefore, we feel from the evidence presented that the sudden onset of aplastic anaemia during treatment with potassium perchlorate cannot be ignored as having a probable direct causal relationship.

Whether in this patient a fatal issue was inevitable after the full development of marrow aplasia is conjectural; but it is felt that the risks of terminal infection might have been reduced by strict isolation and barrier nursing against outside pathogenic organisms.

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Acute Dilatation of Stomach as a Complication of Muscular Dystrophy

Acute dilatation of the stomach is a rare complication in muscle dystrophy. Bevans (1945) reported the cases of four patients with progressive muscular dystrophy who came to necropsy, and in two of them there was marked dilatation of the stomach, with perforation in one. Sections of the stomach in one of her cases showed the changes in the muscle layer which have been described in progressive muscular dystrophy—namely, great variation in the size and shape of the fibres, vacuolation, and clumping of the sarcoplasm, with proliferation of the nuclei of the sarcolemma. These were not considered specific, although it is suggested that they are comparable in many ways to those seen in the skeletal muscles. It would appear from her post-mortem findings that the changes which occur in the skeletal muscle in progressive muscular dystrophy may also occur in the myocardium, the striated muscle of the tongue, oesophagus, and the gastro-intestinal tract.

The following case is regarded as of sufficient rarity to be placed on record.

CASE REPORT

A boy aged 9, a known case of muscular dystrophy of the Leyden-Moebius type, was being treated at home by mucopolysaccharides. He was admitted to the paediatric ward of the City General Hospital, Stoke-on-Trent, on January 3, 1960, complaining that two days previously he had developed a sore throat, followed by generalized abdominal pain and vomiting. He had had no food, and his bowels had not been opened for the three days prior to admission.

On admission he was dehydrated, his eyes were sunken, and his tongue was coated. His urine contained albumin. He was given an enema with a poor result. At 5 p.m. the same day he began to vomit profusely, and the vomit was coffee-ground in nature. His general condition became worse; he complained of a colicky pain and his pulse increased to 148. His temperature was 99.2° F. (37.3° C.). At 6 p.m. he was started on an intravenous drip of N/5 saline, and gastric suction was instituted. He was thought to have intestinal obstruction, and I was asked to see him at 6.30 p.m.

On examination his abdomen was not distended. There was no increase in peristalsis on auscultation of his abdomen, but large quantities of fluid, which were of the classical "peat-laden stream" appearance, were being aspirated in his gastric suction. A straight *x*-ray film of his abdomen showed no fluid levels or evidence of obstruction. In view of this the diagnosis of acute dilatation of the stomach was made. He was given a transfusion of 2 pints (1,140 ml.) of blood, and an intravenous saline drip after this. His condition now gradually improved, and within 24 hours the suction and the intravenous therapy could be discontinued.

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The Health Committee of London County Council has approved plans for the council's first hostel for the mentally ill to be built specially for that purpose. It will be at Brockley Rise, Lewisham. The three-story building will house 62 patients and will have two single-story wings enclosing a paved and planted court. The estimated cost of the building and of equipment is £93,305.

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